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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,603	12/31/2003	Jian Ling	P-17.111(CON)	1293

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EXAMINER	
DAVIS, DEBORAH A	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 06/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/750,603	LING ET AL.	
	Examiner	Art Unit	
	Deborah A Davis	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4, 6, 8-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-4,6,8-14,20 and 21* is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Prosecution Application

1. The request filed on December 31, 2003 for a Continued Prosecution Application (CPA) based on parent Application No. 09/804,774 is acceptable and a CPA has been established. An action on the CPA follows.

Priority

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Drawings

Applicant's petition to enter color drawings has been accepted.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ann E. Grow (USP#5,866,430) in view of Sharonov et al (Analytica Chimica Acta, 290(1994) pages 40-47) and in further view of Treado et al (USP#6,002,476).

Ann E. Grow teaches a method for determining the reactive capacity of a test sample using Raman scattering (See abstract). The test sample may use a variety of samples, including living cells (col. 33, lines 51-60). Ann E. Grow teaches that Raman analysis may be used in pharmaceuticals (col. 25, lines 46-58). A fingerprint of an analyte may be taken just before it is brought into contact with the material to be analyzed (col. 18 lines 39-50). Raman spectrum can be collected, processed and the measured spectrum can then be compared against a library of model reference spectra to determine the any changes in the sample (col. 17, lines 54-59). In another example, 3-D Raman spectroscopy may be used to detect the drug actinomycin D, which is an antibiotic effective against certain bacteria and highly toxic to humans is known to inhibit the transcription process. Specific changes in the Raman spectra of both the drug and the bioconcentrator are monitored (col. 55, lines 5-14). Raman uses is 3-D spectroscopy to individually or collectively eliminates spectral background noise from unimportant cell constituents thereby enhancing sensitivity of a sample (col. 29, lines 18-27). Ann E. Grow also makes reference to the use of Surface Enhanced Raman Scattering (SERS) for more specificity and sensitivity in combination with using a wide range of wavelengths to enhance the signals of a range of taxonomic markers without the interference from fluorescence background of a sample (col. 55, lines 43-58). In

reference to claim 8, Ann E. Grow teaches that a sample may be immobilized on a support member such as a plate to prevent Raman signals coming from the plate during measuring steps such as allowing radiation to be projected from the underside of the sample, a coating such as Ag (silver) and others may be used (col. 44, lines 7-14).

Ann E Grow does not particularly point out a drug interaction within living cells and measuring drug distribution and interaction.

However, Sharonov et al teaches techniques that include instrumentation allowing the recording of confocal microfluorescence and micro-Raman spectra, for the analysis of antitumour drugs such as doxorubicin and mitoxantrone within living cells (see abstract). It is possible to quantitate the concentration of drugs in different cell components and regions of the cell as recited in claim 21 (page 41, column 1). Sharonov et al concludes that such techniques make it possible to calculate the amount of drug bound in different cell compartments and detect the regions of its heterogeneous accumulation in the same component of the cell which is helpful in analyzing the intracellular accumulation, distribution and efflux of the drugs (see conclusion). The drug mitoxanrone was delivered to treat cancer cells and the images were analyzed as recited in claim 19 (page 44). As recited in claims 20 and 17, drug concentrations in aqueous solutions were determined by their absorbencies at 480 and 610nm (page 41, column 2). The metabolism of the drug was determined when mitoxantrone caused condensation and compaction of chromatin together with disturbances of DNA-protein interactions (page 43, column 2, 3rd paragraph). The local and biochemical pathway of the drug mitoxantrone traps the cleavable complex

between DNA and nucleus-located DNA topoisomerase II (page 44, column 1, paragraph 1). Post treatment and pretreatment images were processed as recited in claim 15 to reduce imaging artifacts include three operations: correction, filtration and mapping. Correction of spectral data was performed on images; the background was calculated for each spectrum of the recorded spectral image, followed by subtraction of the background. Second, the scanning of the laser along the x-axis, leads to differences in time of illumination for the different points on the sample. These artifacts were corrected by normalization of spectra (page 42, column 2, paragraph 3).

Sharonov et al is silent with respect to direct imaging, however, Patrick Treado teaches advantages of chemical imaging based on Raman spectroscopy. Raman chemical imaging measurement identifies the presence and/or location of an analyte species in a sample by imaging at the characteristic analyte Raman spectral bands. In general, it is not necessary to have a complete Raman spectrum at each image pixel in order to obtain meaningful and chemically relevant image contrast (column 3, lines 1-16). Chemical imaging with Raman simultaneously provides the clinician with image information on the size shape and distribution of molecular chemical species present within the sample without staining or modification (column 4, lines 35-45).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Ann E. Grow to include analyzing drug interaction within living cells as taught by Sharonov et al to analyze the drug distribution throughout the cell. This analysis of drug interaction within living cells can be useful in pointing various aspects of problems of cell resistance and drug biological activity (see conclusion). It would have

been further obvious to one of ordinary skill in the art to include the use of direct imaging as taught by Treado in the combination of Ann E. Grow in view of Sharonov et al because direct imaging offers important information about the molecular species such as shape, size and distribution within the sample without the need for staining or modification. One of ordinary skill in the art would have been motivated to do so because Raman chemical imaging can be used to make a rapid and quantitative diagnosis (column 4, lines 35-45).

Response to Arguments

5. Applicant's arguments filed December 31, 2003 have been fully considered but is not found persuasive.

6. Applicant argument that the reference of Ann E. Grow and Sharonov et al does not teach direct Raman imaging.

This argument has been found persuasive, however, a third reference has been provided to address this limitation.

Applicant argues that the reference of Sharonov et al uses fluorescence imaging to determine distribution of anti-tumor drugs within living cells and fluorescence imaging is and Raman imaging are based upon two fundamentally different and independent physical processes.

This argument is not found persuasive because Sharonov et al teaches techniques in evaluating antitumour drugs within living cells utilizing microfluorescence and micro-Raman spectra (see abstract), although Sharonov et al is silent with respect

to direct imaging, the reference of Patrick Treado addresses the advantages to using direct Raman imaging (see above rejection).

7. Applicant argues that the reference of Grow teaches to a large extent the binding interactions in a bio-concentrate, not drug uptake in a living cell.

This argument is not found persuasive because the reference of Grow evaluates analyte complexes in a variety of biological samples, one of such being living cells at predetermined wavelengths using Raman spectral bands (see column 33, lines 51-60 and column 18, lines 4-59). The reference of Sharonov et al addresses drug uptake in living cells.

8. Applicant's Joint Affidavit filed December 31, 2003 have been fully considered but not found persuasive. Applicant argument that the reference of Ann E. Grow and Sharonov et al does not teach direct Raman imaging.

This argument has been found persuasive, however, a third reference has been provided to address this limitation.

Allowable Subject Matter

9. Claims 1-14 and 20-21 are allowed.

10. As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

11. The following is a statement of reasons for the indication of allowable subject matter: The prior art neither teaches or suggests the use of the formula that include a dividing step of post-treatment images by pretreatment fingerprints according to formula s'(x,y)/s(x,y) = K'(x,y)/K(x,) found in independent claim 1.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

A. Otto et al, teaches Raman imaging in living cells, (Journal of Raman Spectroscopy).

B. Beljebbar et al, teaches Raman spectral imaging of cellular interaction of drugs with their targets in living cells, (SPIE-The International Society for Optical Engineering).

C. Whitley et al, teaches Raman imaging in living cells, (SPIE-The International Society for Optical Engineering).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah A Davis whose telephone number is (571) 272-0818. The examiner can normally be reached on 8-5 Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah A. Davis
Remsen Bldg.
June 4, 2004

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SUPERVISORY PATENT EXAMINER
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06/14/04